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Risks Associated with Travelling to High Altitude for Patients with Existing Coronary Artery Disease

Dr. Radha Binod Pal[1], Mainak De[2]

[1]Cardiologist, DM (Cardiology), Department of Cardiology, BSMCH

[2]Perfusionist, B.Sc (Perfusion Technologist), Department of Cardiology, BSMCH

Abstract: ***Tourism to high altitude is very popular which attracts a large number of travellers including healthy as well as individual with compromised health. CAD patients are one of them. So risk assessment for this population travelling to high altitudes is of increasing interest. They also seek advice from physicians. Due to lack of studies, evidence based recommendation is not so easy. The main concern for CAD patients at high altitude is increased workload and decreased oxygen supply to damaged myocardium due to a number of factors like low atmospheric PO_2, increased sympathetic tone, increased heart rate, and endothelial dysfunction of atherosclerotic coronary arteries[1-3]. In this study 6 trials has been reviewed where acute effects on high altitude (ranged in 1000m-4500m) on CAD patients as well as effects after acclimatization were observed. Maximum studies observed increased risk of ischemia whereas some found no significant difference in effects between healthy population and CAD patients. Therefore CAD patients may travel high altitudes only after stabilization of disease, proper exercise tolerance and consider physicians consent. Risks can also be avoided by travelling less than 3500 meter of height. However, if symptoms arise during travelling, continuation of proper medication and descent must be done.***

Keywords: Coronary artery disease (CAD), high altitude, Travel, cardiopulmonary stress test

1. Introduction

Travelling to mountains has always been at the top of attraction of leisure time traveller as well as adventure tourists. In West Bengal, Darjeeling alone gets almost 5,00,000 domestic and 50,000 foreign travellers each year. According to India Tourism Statistics 2015, millions of domestic and foreign travellers annually travel to Assam, Sikkim, Himachal Pradesh, Jammu & Kashmir etc. and the number is continuously growing.

When moving from sea level to high altitude, there are reduction in atmospheric pressure, oxygen pressure, humidity and temperature.

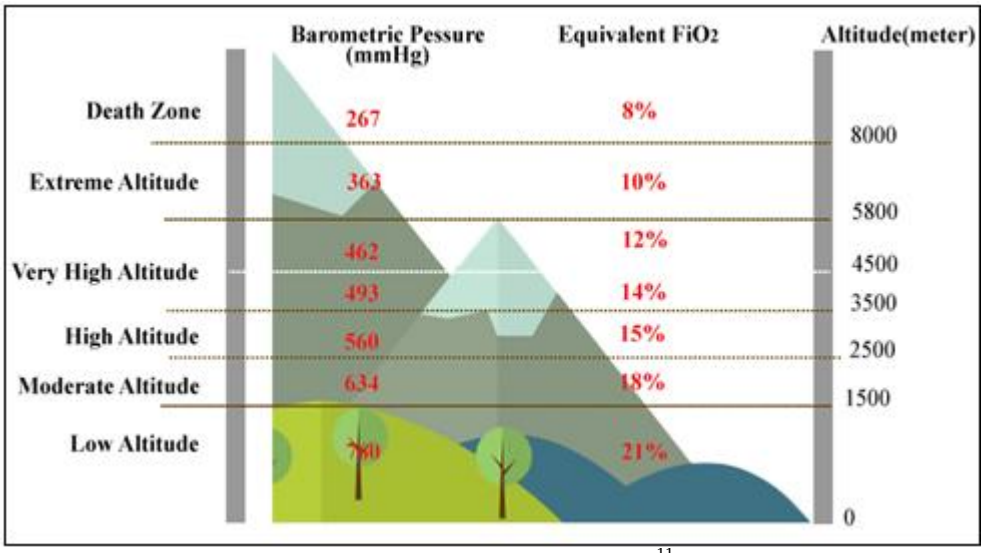

Figure: Classification of altitude[11]

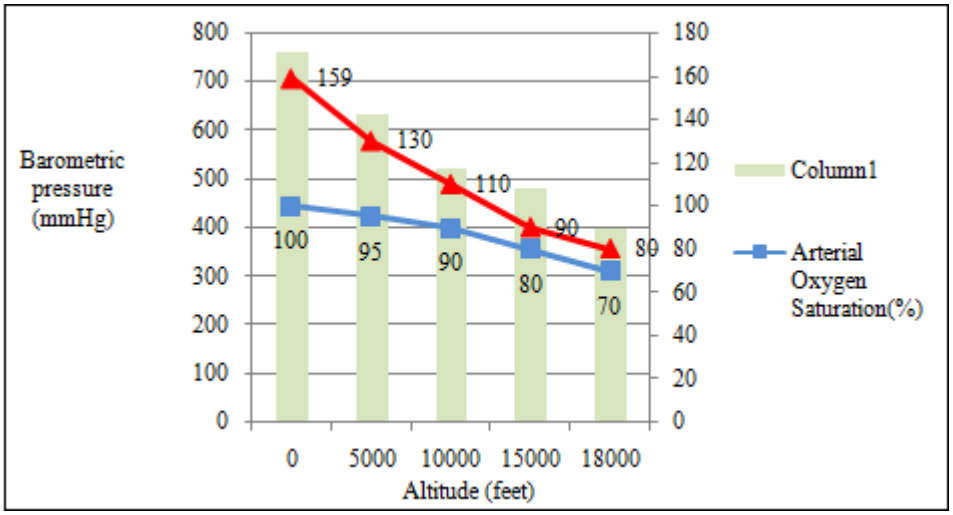

Figure: Changes in barometric pressure, inspired PO_2 and arterial oxygen saturation with altitude

Visiting mountainous regions offers wide range of pleasure which attracts healthy people as well as people with chronic health issues.

One of the top health issues today is Ischemic heart disease or Coronary Artery disease. In fact it is ranked as number 1 among the global causes of death by WHO.

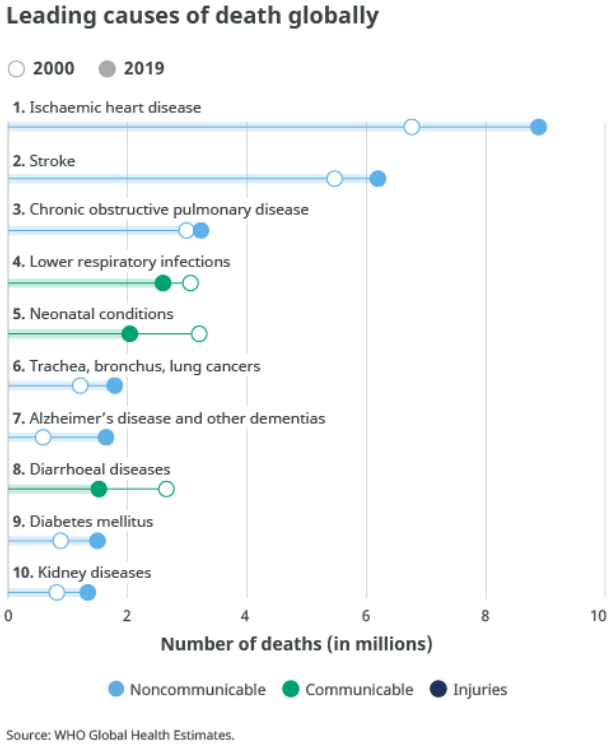

Figure: Ranking of IHD as global cause of death by WHO

Ischemic Heart Disease is defined as acute or chronic form of cardiac disability arising from imbalance between the myocardial supply and demand of oxygenated blood. Since narrowing or obstruction of the coronary arterial system is the most common cause of myocardial anoxia, the alternate term '*Coronary Artery Disease'* is used synonymously with IHD.

To understand the risk factors for these patients if going to high altitude needs a brief discussion about the effect of high altitude on physiology-

Acute effect:

Cardiovascular physiology is most affected during the initial days at high altitude and most of the changes causes increased work load on heart. The sigmoidal oxygen-haemoglobin dissociation curve shows that with reduction in partial pressure of oxygen causes lower oxygen saturation[1]. With increase in altitude arterial oxygen saturation is well maintained due to relatively flat component of the upper part of the curve but above 2500m the steeper section comes in business leading to steep oxygen desaturation. Total oxygen demand of body at a certain workload is independent of altitude, therefore due to decrease in arterial oxygen content, cardiac output must be increased to maintain adequate supply of oxygen to every organ. This cardiac output increases by increasing heart rate as stroke volume does not change significantly with high altitude. Increase in heart rate is related to increased sympathetic activity and vagal withdrawal.

Pulmonary artery pressure is also increased due to hypoxia induced pulmonary vasoconstriction. This may lead to increased right ventricular pressure overload and changes in left ventricular diastolic function[2].

In addition, increased sympathetic tone, arterial hypertension, cold increases LV after load.

Effect on coronary perfusion:

In high altitude myocardial oxygen demand is increases due to increased workload on heart. In healthy individual hypoxia induces coronary vasodilatation to increase coronary blood flow to balance myocardial oxygen supply and demand. But in atherosclerotic coronary arteries of CAD patient, endothelial dysfunction may lead to paradoxical hypoxia related vasoconstriction, which worsens myocardial oxygen supply and demand balance[3].

Effect after long-term exposure:

After long-term high altitude exposure acclimatization occurs which causes physiological compensatory mechanisms to set in and leads to lower blood pressure, lower cardiac output, increase in RBC count and decrease in alveolo-arterial oxygen gradient[4]. However it is not well established if these changes are sufficient for CAD patients at as high altitude as 3500 m or above.

2. Objective

When CAD patients are going to high altitude, they may ask for advice but due to lack of studies counselling of these patients is not easy. The purpose of this study is to perform systematic and evidence based review of available literature about the effect of high altitude on patients with known CAD to help physicians to some extent in making their recommendations.

3. Methods

Search strategy
Literature search was done via Google under the key words high altitude, CAD patients, travel, physiology (As single or in combinations). Duplicates, editorials and letters to the editors were excluded. Studies from all over the world were included.

Data extraction:
From each literature meeting inclusion criteria, the following points were extracted: first author, journal, year of publication, sample size, outcome, and recommendations (if any).

Analysis:
All six literatures were analysed by two individual authors. Each and every result came out from analysing data were discussed. Points of disagreements were sorted out and ultimate conclusion was made by consensus.

4. Result

Total 6 trials were found that met inclusion criteria[5-10]. Sample size ranged from 9 to 46. Four studies were done by taking the subjects to a high location, study was done by artificially creating the atmosphere like a location at2500m and 4500m height and another study used both strategy of artificially creating an atmosphere like 2500m and after that also trialled same individual at a real location at 2500m. In former 4 studies trials were done at 1000m, 2500m, 3100m, 3454mand 4200m. No incidents of mortality are reported in these studies. Almost all the studies observed increase in blood pressure especially systolic at some stages during stress test at high altitude.J-P schmid et al. and Benjamin D. Levine et al. observed increased heart rate at high altitude where as Jörg Erdmann et al observed lower heart rate at rest at high altitude. Benjamin D. Levine et al got one individual in their study group who sustained a MI after his exercise test at high altitude.

Table: Summary of the studies

Details of study reviewed						
	Authors	Sample size	Age & Sex	About subjects studied	Altitudes at which tests were done	Tests done
1	J-P Schmid et al[5]	22	57 y (mean age), 20 male & 2 female	15 with STEMI & 7 with NSTEMI; 6 with TVD, 6 with DVD, 10 with SVD; 15 had CABG & 7 had PTCA	First at sea level then at 3454m from sea level	Symptom limited cardiopulmonary stress test; tests were done within 1-3 hours of reaching the altitude. (β blockers were stopped 5 days before the test for the whole testing period)
2	B. J. Morgan et al.[6]	9	50-75y, all male	5 with previous MI among whom 2 underwent CABG, 3 with stable angina and 1 with ST depression on exercise ECG	first at sea level, second at 1600m and third test at 3100m from sea level	Symptom limited treadmill test
3	J. Erdmann et al.[7]	46	35-65y, all male	Group N(n=23), none had any cardiovascular disease. Group H(n=230, all hade documented CAD with history of MI and/or revascularization within past 4 months from the study	First at 1000m and second at 2500m from sea level	Symptom limited bicycle stress test
4	Benjamin D. Levine et al.[8]	20 (all were veterans or spouses of the US Army 10th mountain division)	mean 68±3 y	7 of 20 had CAD(2 CABG, 2 PTCA & 3 MI without revascularization	Day 1 & Day 2: at sea level Day 3: acute simulated high altitude at hypobaric chamber that was decompressed to a simulated altitude of 2500m, barometric pressure 560m, temp 20-22°C) At 1-4 wks: 2500m	Basic examination, symptom limited treadmill stress test
5	Christophe A. Wyss et al.[9]	18	Mean 23±2 y, all male	Control group(n=10) had all healthy acclimated patient; Patient group(n=8) had all CAD patients (3 with 1 vessel, 4 with 2 vessel & 1 with3 vessel involvement)	Altitude was simulated by inhalation of hypoxic gas (16.5% O_2 12.5% O_2 resulting in O_2 pressure of 119mmHg & 90mmHg, which corresponds to altitudes of 2500m & 4500m) (oncly control group was exposed to 4500m whereas the patient group was only exposed to 2500m)	With subject's feet attached to a bicycle ergometer, myocardial blood flow(MBF) was measured at rest. Then adenosine was infused for 7 minutes at 140µg/kg/min. 3 mins after starting infusion hyperemic MBF measurement was started. After 10 min exercise was started and MBF was

						measured immediately after end of exercise
6	S. T. de Vries[10]	15	patient group: mean 53±8 y; 7M & 1F Control group: mean 41±16 y; 4M & 3F	Control group(n=7) had all healthy individual, Patient group(n=8) had all CAD patients	Sea level in Nov. 2006, at 4200m in March 2007acutely & after 2 weeks of acclimatization	Symptom limited cardiopulmonary test and echocardiography after stress test

Results of the studies

	Authors	Result
1	J-P Schmid et al.[5]	1. Systolic blood pressure was higher during some stages of study at 3454m 2. Increase in heart rate by 19% compared with that at low altitude (p value < 0.001) 3. VO2max was increased equally during submaximal exercise at both altitude but at 3454m it increased less steeply with increase in workload (p value < 0.001). 4. At every stage lactate concentrations were higher at 3454m, except for the maximum value. At maximal exercise, lactate concentrations were 7.1mmol/L at 540m and 6.9mmol/L at 3454m (p value = 0.715 i.e. statistically insignificant). Despite this changes, no complications were observed in terms of stress related ischemia or arrhythmias.
2	B. J. Morgan et al.[6]	1. Minute ventilation was higher during submaximal workload at 3100m (p value < 0.05) 2. Oxygen saturation was decreased both during rest and work at 3100m 3. HR was higher at 3100m but there was no change in maximum HR or HR at the onset of angina or ST segment depression 4. Two patient reported shortness of breath after arrival at 3100m
3	J. Erdmann et al.[7]	Group N 1. Blood pressure value did not differ 2. Resting heart rate was lower at 2500m but HR during exercise was not different 3. Oxygen saturation was lower at 2500m 4. Endurance was significantly decreased Group H 1. Blood pressure increased (increase in SBP > increase in DBP) 2. Oxygen saturation tended to be lower at 2500m 3. There was trend toward lower heart rate at 2500m 4. The accomplished amount of watts decreased by 2.7%
4	Benjamin D. Levine et al.[8]	1. HR at rest increased slightly acutely and remained slightly elevated after 5 days of acclimatization 2. SBP & DBP decreased ċ acute exposure and returned to baseline afteracclimatization 3. Cardiac output was acutely increased by 14%. With acclimatization fell below baseline 4. VO_2max decreased by 11% with acute altitude exposure 5. One patient sustained a MI after his exercise test after acclimatization
5	Christophe A. Wyss et al.[9]	1. In both group heart rate and rate pressure product (RPP) increased significantly during hypoxia. The adenosine induced increase in RPP during hypoxia was more pronounced in CAD patients. 2. In healthy subjects resting and even more pronounced exercise induced MBF increase at high altitudes, indicating a maintained exercise induced reserve upto 4500m. By contrast, in patients with CAD, compensatory mechanisms appear to be exhausted even moderate altitude, because their bicycle exercise-induced reserve was decreased even at 2500m
6	S. T. de Vries[10]	1. Significant increase in RV diameter in both group at 4200m 2. significant decrease in tricuspid annular plane systolic excursion (TAPSE) at high altitude 3. Mild LV diastolic dysfunction at high altitude in both group

5. Discussion

In all the five studies reviewed they compared effect of exercise stress test at sea level and at high altitudes. Changes at rest at high altitude were also observed.

In the first study reviewed, J-P Schmid et al took their patient group from Switzerland (540m) to Jungfraujoch (3454m). All the patients were revascularised either by PTCA or CABG and had ejection fraction > 45%. *They stopped beta blockers 5 days before the test for whole study period*. Effect of stress on heart by comparing rest and exercise at both altitudes were studied. They observed increased in heart rate by 19% at high altitude during exercise, increased systolic BP at various stages of stress test at 3454 m but no significant difference in SBP and DBP at maximal exercise in both locations, decrease in VO_2max by 19% at exhaustion and increase in blood lactate level. Clearly increase in heart rate is a compensatory mechanism by heart to maintain O_2 supply to body. Hypertension due to increased sympathetic tone induced by hypoxia indicates increased myocardial oxygen demand. But decrease in VO_2max and increased blood lactate level indicates towards the lack of oxygen supply to already damaged myocardium.

This study indicates that CAD patients travelling to high altitude may experience worsen ischemia or potentiate acute MI during physical activities.

There were some limitations of this study. The first being study population only consisted of only patients with revascularised stable CAD without a relevant reduction in LV function. Other one was the environment during exercise testing was well controlled. So under outdoor environmental stress and sustained physical activity may effect differently.

In the second trial by B. J. Morganet al, they also observed higher heart rate at rest and submaximal workload and lower oxygen saturation at higher altitudes. Exercise duration was reduced by 1-3 min at high altitude. According to their observation Ischemic endpoint occurred at the same heart rate systolic blood pressure product at high altitudes. But the ischemia endpoint was reached at a lower workload at high altitude. This study also indicates toward decreased exercise tolerance capacity for CAD patients at high altitudes. They observed change in haematocrit with high altitude. In pulmonary function they have noted reduced forced vital capacity with higher altitude. In their study population two patient reported shortness of breath after arrival at 3100m.

In the next study Jörg Erdmann et al compared effect of high altitude on 23 normal individual with 23 patients who had documented CAD with a history of MI and/or revascularization within the past 4 months and LV ejection fraction ≤ 45% as evidence after acute incident and within 3 months of the study. They observed increase in blood pressure, contrasting lower heart rate at rest at high altitude and they have explained it by an initial increase in vagal tone after exposure to altitudes. They also observed lower oxygen saturation at rest and during exercise at higher altitude but this pattern was same for both group of population. Maximum workload in terms of watt was also lowered by 4% at higher altitude though no ischemic events occurred during stress test.

Their study also had some limitation. Firstly in terms of patient selection, they only selected middle aged men with good working capacity despite impaired LV function and no signs of residual ischemia. Secondly, they perform exercise test indoors. And lastlyonly acute effects were studied(within the first hours after ascent).

The next study was by Benjamin D. Levine in which they observed increased heart rate, cardiac output, decreased saturation and blood pressure and decreased VO_2max. They observed the double product 9heart rate 8 systolic blood pressure, a measure of myocardial oxygen demand) was 5% less and systemic workload was 8% less for inducing 1mm ST depression at higher altitude. One of their patient sustained MI after exercise test at high altitude.

In the next study by Christophe wyss et al. they simulated atmosphere like 2500m and 4500m by inhalation of hypoxic gas. They studied the effect on CAD patients (*stable CAD in the Canadian Cardiovascular Society functional class II to III with mild[>50%-70%] to moderate [>70%-90%] occlusion*) at 2500 m in comparison to control group at 4500m. In healthy subjects resting and even more pronounced exercise induced MBF increase at high altitudes, indicating a maintained exercise induced reserve up to 4500m. By contrast, in patients with CAD, compensatory mechanisms appear to be exhausted even moderate altitude, because their bicycle exercise-induced reserve was decreased even at 2500m.

In the last study S. T. De Vries et al compared 8 CAD patients to 7 healthy subjects at high altitude by symptom limited cardiopulmonary stress test and echocardiographical evaluation of cardiac morphology and function. According to their findings cardiac morphology and function do not differ substantially in low risk patients with CAD in comparison to healthy controls and also changes seem to be in normal range of physiological adaptation to high altitude. Point to be noted is unlike Schmid et al *they didn't stop beta blockers during the study.*

They also recommended that low risk patients can ascent 3000-3500m height with minimal increased risk, provided that the exercise capacity at sea level is satisfactorily high and there is no concomitant illness impairing normal oxygenation of blood. They also recommended slow ascent or an acclimatization period of 3-5 days to guard against worsening of angina and concluded that if symptoms of ischemia or heart failure do arise on ascent medication can help, but descent itself is the fastest and most efficient treatment.

6. Recommendations from different studies

1) Almost all the articles available suggests that patients with history of CAD can safely ascend upto 3500m from sea level safely. Gianfranco Parati et al. in their clinical recommendation for high altitude exposure of individuals with pre-existing CAD stated that low risk CAD group (CCS 0-I) may safely ascend upto 4200m from sea level and perform light to moderate physical activity. CCS II-III with moderate risk can ascend upto 2500 m but with physical activity heavier than lighter is contraindicated. Whereas for CCS IV with high risk are recommended not to ascend to high altitude[11].
2) According to Schmid et al. exposure to high altitude can be safe after atleast 6 months of acute coronary event with appropriate rate pressure product during stress test (atleast 25000mmHg * beats/min).[5]
3) B.J.Morgan et al. and Benjamin D Levine observed higher heart rate at high altitude with decreased exercise tolerance. Almost 90% of available literature supports this data. C. Denhert. Et al recommended use ofcombined alpha and beta blocking agents (carvedilol, labetolol) can be helpful in regulating heart rate and BP[3].
4) M. Burtscher et al in their observation on sudden cardiac death during mountain hiking noted that in 54% cases individuals were suffering from hypercholesterolemia which is a very significant percentage. Therefore patients with history of CAD should be allowed for high altitude exposure with controlled lipid profiles and continued HMG CoA reductase inhibitor (statins).
5) Effect of high altitude on risk of plaque rupture is unknown. There are some literature (T. Lehmann et al., A. S. Rocke et al[12]) suggests exposure to high altitude induces platelet activation and aggregation. Along with platelet hyperactivity increased B.P and shear forces, changes in arterial tone and twisting has been given liability for increased risk of plaque rupture in high altitude. Therefore it can be recommended that antiplatelet agents must be continued but requirement of switching to dual antiplatelet agents in patients who are in single antiplatelet at sea level is unknown. But patients with continued dual antiplatelet agent should be

involved in limited activity to avoid any injury as they have high risk of bleeding.

6) Gianfranco Parati et al. also mentioned as acetazolamide seems to reduce the risk of sub endocardial ischemia at high altitude in healthy subjects, thus use of that for AMS prevention can be helpful. Though they also mentioned that there is lack of evidence about its benefit on CAD patiets.[11]

7. Conclusion

The studies reviewed suggest that high altitude causes stress to already damaged heart. Generally CAD patients should not go to high altitudes in unstable disease states. Once stable and well compensated with physicians consent and proper exercise capacity testing they can travel to high altitudes, provided continuation of proper medication and limitation of physical activity. However there is lack of data, they must not ascend above 3500m. For safe stay above 3500 m along with stable disease, increased exercise capacity than normal is also required.

But we felt there is a lack of data about alterations in medications, as well as in some aspects of physiological changes that occur in HA like plaque behaviour. Therefore more studies are required focusing on those aspects to make a proper guideline for improving quality of life and increased exercise tolerance for CAD patients at high altitude.

Disclosures:
There are no conflicts of interest or financial ties to be disclosed.

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Author Profile

Dr. RadhaBinod Pal, MD (Paed.), DM (Cardiology), Consultant cardiologist, Bankura Sammilani Medical College & Hospital
Email ID: rbinod100@gmail.com

Mr. Mainak De, B.Sc (Perfusion Technology),Clinical Perfusionist, Bankura Sammilani Medical College & Hospital
Email ID: mainakde97@gmail.com